Effects of Risperidone on Phencyclidine-Induced Behaviors: Comparison with Haloperidol and Ritanserin

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ABSTRACT—In this study, we investigated whether risperidone, a serotonin-S2A (5-HT2A)/dopamine-D2 (D2)-receptor antagonist, inhibits phencyclidine (PCP)-induced stereotyped behaviors in comparison with haloperidol and ritanserin. Moreover, we also attempted to investigate the effects of these antipsychotics on the contents of dopamine, serotonin (5-HT) and their metabolites in rat striatum and frontal cortex. In rats, PCP (5 mg/kg, i.p.) caused hyperlocomotion and stereotyped behaviors, including sniffing, head-weaving, backpedalling and turning. Both risperidone (0.8–2.4 mg/kg, p.o.) and haloperidol (0.3–1.0 mg/kg, p.o.) inhibited these behaviors, except for backpedalling, in a dose-dependent manner. PCP (10 mg/kg, i.p.) produced hyperlocomotion and stereotyped behaviors, including rearing, sniffing head-twitch, backpedalling and turning. Risperidone (0.8–2.4 mg/kg, p.o.) inhibited both hyperlocomotion and PCP-induced behaviors, except for backpedalling, while ritanserin (3–10 mg/kg, p.o.) inhibited only the head-twitch. These results suggest that risperidone may have an antipsychotic effect on schizophrenia as well as PCP psychosis in humans by exerting a mixed 5-HT2A/D2 antagonism. Neurochemically, the increasing effects of risperidone on the content of DOPAC and the ratio of DOPAC to dopamine in the striatum were lower than those of haloperidol. These findings may support the view that the extrapyramidal side effects of risperidone are lower than those of haloperidol in clinical situations.

Keywords: Risperidone, Mixed 5-HT2A/D2 antagonist, Phencyclidine, Stereotyped behavior

It is well known that typical antipsychotics have beneficial effects on the positive symptoms of schizophrenia, but not on the negative symptoms (1). Many investigators have already reported that the blockade of both dopaminergic and serotonergic neuronal systems may be important for the treatment of both positive and negative symptoms of schizophrenia: clinically, 1) clozapine and setoperone, both which are potent serotonin-S2A (5-HT2A)-receptor antagonists with a relatively lower dopamine-D2 (D2)-receptor antagonistic property, are effective in both the positive and negative symptoms of schizophrenia (2–4), and 2) ritanserin, a 5-HT2A-receptor antagonist, reinforces the antipsychotic effects of haloperidol, particularly on the negative symptoms (5).

In normal individuals, phencyclidine (1-(1-phenylcyclohexyl)piperidine hydrochloride, angel dust, PCP) induces a schizophrenia-like syndrome including both positive and negative symptoms (6, 7). Therefore, PCP may provide a good animal model of schizophrenia that includes the negative symptoms (7–9).

In animals, PCP causes stereotyped behaviors (10–12) as other psychostimulants do. In previous experiments, we reported that the hyperlocomotion and some of stereotyped behaviors induced by PCP were mediated by dopaminergic and serotonergic neuronal systems and that PCP-induced head-twitch via 5-HT2A receptors in rats (13–16). Therefore, several investigators including us hypothesized that the drugs that block both PCP-induced dopamine- and 5-HT-mediated stereotyped behaviors may possibly prevent both the positive and negative symptoms of schizophrenia (7–9).

Risperidone is a potent D2-receptor antagonist with a predominant, concomitant 5-HT2A antagonistic activity (17, 18). In clinical use, it has been reported that risperidone improves both the negative and positive symptoms of schizophrenia with the relative absence of extrapyramidal side effects (19).

In this study, we investigated whether the concomitant
blockade of D_{2}-receptors and 5-HT_{2A}-receptors by risperidone inhibits PCP-induced stereotyped behavior in rats in comparison with the D_{2}-receptor antagonist haloperidol and the 5-HT_{2A}-receptor antagonist ritanserin. Moreover, we attempted to investigate the effects of these antipsychotics on the contents of monoamines and their metabolites in the rat striatum and frontal cortex.

**MATERIALS AND METHODS**

**Animals**

Male Kbl Wistar rats (Oriental Bio Service Co., Ltd., Kyoto), weighing 200 to 300 g, were used. The animals were maintained in a temperature- and humidity-regulated room (22–24°C, 55±5%) with controlled lighting (light on 9:00 to 21:00) for at least 3 days before the experiment.

**Drugs**

The following drugs were used: phencyclidine hydrochloride (PCP, synthesized by us) was dissolved in 0.9% saline. Risperidone (Janssen Kyowa, Tokyo) and ritanserin (Janssen Kyowa) were dissolved in distilled water containing 2 equivalents of tartaric acid. Haloperidol (Sigma, St. Louis, MO, USA) was dissolved in distilled water containing an equivalent of tartaric acid. In the behavioral study, PCP was injected i.p. (0.2 ml/100 g body weight) and the other drugs and vehicle were given p.o. (0.2 ml/100 g body weight) 1 hr before the injection of PCP.

**Behavioral studies**

All behavioral experiments were conducted between 11:00 and 19:00; the room temperature was 22–24°C. Animals were observed while they were in individual plastic cages (30 × 35 × 17 cm). Over 2 hr after the habituation to the test room and food-deprivation, they were habituated to the cages by placing them individually for 30 min before the experiments. The animals were assigned randomly to the different drug treatment groups.

**Measurement of PCP-induced hyperlocomotion and stereotyped behaviors**

Nabeshima et al. (8) reported that head-weaving, which was partly mediated by both dopaminergic and serotonergic neuronal systems, was observed in rats treated with PCP at 5 mg/kg, i.p., but scarcely seen in those treated with PCP at 10 mg/kg, i.p. In contrast, they found that head-twitch, which was mediated by 5-HT_{2A}-receptors, occurred in rats treated with PCP at 10 mg/kg, i.p., not with PCP at 5 mg/kg, i.p. Therefore, we selected 2 different doses of PCP: PCP at 5 mg/kg, i.p. was used to evaluate the blocking effects of risperidone and haloperidol on the head-weaving, and PCP at 10 mg/kg, i.p. was used to evaluate the blocking effects of risperidone and ritanserin on head-twitch. Other behaviors (hyperlocomotion, rearing, sniffing, backpedalling and turning) were measured in rats treated with both doses of PCP, because the effects of risperidone on them were compared to those of haloperidol and ritanserin.

Rats were challenged with PCP (5 or 10 mg/kg, i.p.) 1 hr after pretreatment with vehicle or drugs; and then the hyperlocomotion and stereotyped behaviors, i.e., rearing, sniffing, head-weaving, head-twitch, backpedalling and turning were measured for 90 min as described by Nabeshima et al. (8, 15). Briefly, hyperlocomotion was measured automatically over a 90-min period by using electric digital counters with infrared cell sensors placed on the walls (SCANET SV-10; Toyo Sangyou, Toyama). The stereotyped behaviors were rated as follows: rearing (number of times the animal stood on its hind legs), sniffing (0, absent; 1, occasional; 2, frequent; 3, constant), head-weaving (number of times the animal made slow, side-to-side head movements), head-twitch (number of times the animal exhibited rapid lateral twitching of the head similar to the pinna reflex), backpedalling (number of times the animal made backward locomotion), and turning (the number of times the animal circled laterally to the left or right over 360° within a relatively small area). Rating for rearing, backpedalling and turning was made over a 90-min observation period. Rating for head-weaving and head-twitch was made over a 3-min observation period every 15 min for 78 min postinjection. Sniffing was scored over a 1-min observation period every 15 min for 76 min postinjection. The doses of oral administration for haloperidol and ritanserin were approximately fixed at the doses that inhibited methamphetamine-induced hyperactivity (20) and (±)DOI ((±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane)-induced head-twitch (21), respectively. In preliminary experiments, we investigated the effects of several doses of three antipsychotics, and then selected slightly and markedly inhibitory doses of haloperidol and ritanserin on PCP (5 mg/kg, i.p.),-induced hyperlocomotion and PCP (10 mg/kg, i.p.)-induced head-twitch, respectively. The doses of risperidone were selected in the same way.

**Determination of dopamine and 5-HT and their metabolites in rat brain**

The doses of antipsychotics were fixed as follows: 2.4 mg/kg for risperidone, 1.0 mg/kg for haloperidol and 10 mg/kg for ritanserin, because these doses had similar effects on the PCP-induced behaviors; the effects of risperidone (2.4 mg/kg) on some PCP-induced behaviors and head-twitch were almost equal to those of haloperidol (1.0 mg/kg) and ritanserin (10 mg/kg),
respectively. Rats were injected i.p. with PCP (10 mg/kg) or the vehicle 1 hr after the p.o. treatment with antipsychotics and decapitated 1 hr after the injection of PCP. The striatum and frontal cortex were dissected out. The samples were rapidly frozen and stored in a deep-freezer at -80°C until the measurement of the monoamines and their metabolites. The content of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in the striatum and frontal cortex was determined by high performance liquid chromatography (HPLC) with electrochemical detection according to the method of Nitta et al. (22).

**Statistical analyses**

For the data of hyperlocomotion, rearing, head-weaving, head-twitch, turning and biochemical data, overall group differences between the control and drug-treated groups were determined by one-way analysis variance of ranks (ANOVAs) and the parametric Tukey test. For the data of sniffing, overall group differences between the control and drug-treated groups were determined by the Kruskal-Wallis analysis of variance of ranks. Statistical analysis was then carried out by the non-parametric Tukey test for data in which the Kruskal-Wallis H scores were associated with a probability of less than 5%.

**PCP 5 mg/kg**

**Fig. 1.** Effects of risperidone and haloperidol on PCP (5 mg/kg, i.p.)-induced hyperlocomotion (A) and turning (B) in rats. Rats were challenged with PCP 60 min after the p.o. treatment with vehicle, risperidone or haloperidol, and then hyperlocomotion and turning were measured for 90 min. Each column represents the mean ± S.E. from 9 to 15 rats. Motility counts of the vehicle + saline-treated group were 1324 ± 350. *P < 0.05, **P < 0.01 vs. vehicle-treated group (Tukey test).

**Fig. 2.** Effects of risperidone and haloperidol on PCP (5 mg/kg, i.p.)-induced sniffing (A) and head-weaving (B) in rats. Rats were challenged with PCP 60 min after the p.o. treatment with vehicle, risperidone or haloperidol, and then sniffing and head-weaving were measured for 90 min. Each point represents the mean from 8 rats. ○: vehicle; □: risperidone, 0.8 mg/kg; ■: risperidone, 2.4 mg/kg; △: haloperidol, 0.3 mg/kg; ▲: haloperidol, 1.0 mg/kg. *P < 0.05, **P < 0.01 vs. vehicle-treated group (Tukey test).
RESULTS

Effects of risperidone and haloperidol on PCP (5 mg/kg, i.p.)-induced hyperlocomotion and stereotyped behaviors in rats

PCP (5 mg/kg) produced locomotor stimulation (hyperlocomotion), but not rearing. PCP (5 mg/kg)-induced hyperlocomotion was inhibited by risperidone (0.8 and 2.4 mg/kg) and haloperidol (0.3 and 1.0 mg/kg) in a dose-dependent manner (Fig. 1A) without affecting PCP-induced ataxia (data not shown). Risperidone (2.4 mg/kg) and haloperidol (1.0 mg/kg) produced significant

PCP 10 mg/kg

A. Sniffing

B. Head-twitch

Fig. 3. Effects of risperidone and ritanserin on PCP (10 mg/kg, i.p.)-induced hyperlocomotion (A), rearing (B) and turning (C) in rats. Rats were challenged with PCP 60 min after the p.o. treatment with vehicle, risperidone or ritanserin, and then hyperlocomotion, rearing and turning were measured for 90 min. Each column represents the mean±S.E. from 8 to 12 rats. Motility counts and number of rearings of the vehicle+saline-treated group were 1128±426 and 7.6±3.6, respectively. *P<0.05, **P<0.01 vs. vehicle-treated group (Tukey test).

Fig. 4. Effects of risperidone and ritanserin on PCP (10 mg/kg, i.p.)-induced sniffing (A) and head-twitch (B) in rats. Rats were challenged with PCP 60 min after the p.o. treatment with vehicle, risperidone or ritanserin, and then sniffing and head-twitch were measured for 90 min. Each point represents the mean from 6 rats.

○: vehicle; □: risperidone, 0.8 mg/kg; ■: risperidone, 2.4 mg/kg; △: ritanserin, 3 mg/kg; ▲: ritanserin, 10 mg/kg. *P<0.05, **P<0.01 vs. vehicle-treated group (Tukey test).
effects. Moreover, risperidone (0.8 and 2.4 mg/kg) and haloperidol (1.0 mg/kg) reduced the score for PCP-induced turning (Fig. 1B). However, these drugs failed to inhibit the backpedalling induced by PCP (data not shown). In addition, PCP (5 mg/kg)-induced sniffing and head-weaving were also inhibited by risperidone and haloperidol (Fig. 2, A and B). The treatment of these antipsychotics failed to affect the locomotion and the score of rearing and sniffing of naive rats (data not shown).

Effects of risperidone and ritanserin on PCP (10 mg/kg, i.p.)-induced hyperlocomotion and stereotyped behaviors in rats

As shown in Fig. 3A, the hyperlocomotion induced by PCP (10 mg/kg) was inhibited by risperidone (0.8 and 2.4 mg/kg) in a dose-dependent manner, but not ritanserin (3 and 10 mg/kg) and both antipsychotics failed to affect PCP-induced ataxia (data not shown). Risperidone (0.8 and 2.4 mg/kg) reduced the score for PCP (10 mg/kg)-induced rearing (Fig. 3B), turning (Fig. 3C) and sniffing (Fig. 4A). In contrast, the score for PCP-induced

| Table 1. Effects of risperidone, haloperidol and ritanserin in combination with saline or PCP (10 mg/kg, i.p.) on the contents of monoamines and their metabolites and monoamine turnover in the striatum |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug treatment  | The contents of monoamines and their metabolites (ng/g wet weight) | Monoamine turnover |  |
|                 | dopamine | DOPAC | HVA | 5-HT | 5-HIAA | DOPAC/dopamine | HVA/dopamine | 5-HIAA/5-HT |
| Saline treatment |         |       |     |      |        |              |              |            |
| Vehicle         | 12179±665 | 1220±5  | 763±45 | 934±61 | 821±92 | 0.100±0.003  | 0.063±0.003 | 0.877±0.074 |
| Risperidone 2.4 mg/kg | 11648±394 | 3471±248* | 2534±139* | 817±38 | 874±53 | 0.297±0.012* | 0.217±0.007* | 1.076±0.077 |
| Haloperidol 1.0 mg/kg | 11139±918 | 3746±324** | 2345±248** | 892±41 | 864±41 | 0.346±0.044** | 0.218±0.033** | 0.970±0.021 |
| Ritanserin 10 mg/kg | 11899±114 | 1374±174 | 817±28 | 904±69 | 804±15 | 0.115±0.015  | 0.069±0.003 | 0.902±0.054 |
| PCP treatment   |         |       |     |      |        |              |              |            |
| Vehicle         | 12113±364 | 1325±24 | 876±54 | 916±65 | 883±39 | 0.110±0.005  | 0.073±0.006 | 0.971±0.038 |
| Risperidone 2.4 mg/kg | 10273±471 | 3931±306** | 2687±380** | 873±25 | 969±9  | 0.382±0.023** | 0.260±0.029** | 1.113±0.041 |
| Haloperidol 1.0 mg/kg | 10146±603 | 5016±314** | 3354±17** | 745±44 | 964±8  | 0.494±0.002** | 0.333±0.018** | 1.302±0.071** |
| Ritanserin 10 mg/kg | 12047±724 | 1332±154 | 838±109 | 950±46 | 932±38 | 0.110±0.006  | 0.069±0.006 | 0.985±0.035 |

Rats were injected i.p. with or without PCP (10 mg/kg) 1 hr after p.o. treatment with antipsychotics and then decapitated 1 hr after the injection of PCP. The striatum was dissected out. The contents of monoamines and their metabolites were determined by HPLC with electrochemical detection. Each value represents the mean±S.E. from 3 to 4 rats. *P<0.01 vs. the corresponding vehicle-treated group (Tukey test).

| Table 2. Effects of risperidone, haloperidol and ritanserin in combination with saline or PCP (10 mg/kg, i.p.) on the contents of monoamines and their metabolites and monoamine turnover in the frontal cortex |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug treatment  | The contents of monoamines and their metabolites (ng/g wet weight) | Monoamine turnover |  |
|                 | dopamine | DOPAC | HVA | 5-HT | 5-HIAA | DOPAC/dopamine | HVA/dopamine | 5-HIAA/5-HT |
| Saline treatment |         |       |     |      |        |              |              |            |
| Vehicle         | 3.5±1.2 | 49.6±8.2 | 16.4±3.2 | 185.2±13.2 | 125.0±11.5 | 0.066±0.012 | 0.355±0.103 | 0.673±0.016 |
| Risperidone 2.4 mg/kg | 3.2±0.2 | 35.0±4.5 | 31.6±4.7 | 190.7±21.0 | 136.1±14.3 | 0.095±0.012 | 0.895±0.036* | 0.716±0.025 |
| Haloperidol 1.0 mg/kg | 3.6±0.2 | 28.6±4.9 | 31.1±2.0 | 187.9±10.1 | 113.4±11.2 | 0.135±0.021 | 1.144±0.188** | 0.608±0.070 |
| Ritanserin 10 mg/kg | 2.2±0.1 | 31.4±4.2 | 11.2±3.8 | 206.8±10.7 | 124.1±7.3 | 0.077±0.014 | 0.328±0.086 | 0.603±0.035 |
| PCP treatment   |         |       |     |      |        |              |              |            |
| Vehicle         | 2.2±0.3 | 29.3±4.0 | 16.9±1.8 | 211.8±9.1 | 133.9±4.1 | 0.080±0.024 | 0.599±0.106 | 0.634±0.029 |
| Risperidone 2.4 mg/kg | 5.0±0.8 | 28.9±5.7* | 46.2±13.1* | 227.5±18.4 | 154.3±14.5 | 0.172±0.013* | 1.556±0.425* | 0.833±0.048 |
| Haloperidol 1.0 mg/kg | 4.3±0.4 | 32.7±3.3 | 44.1±4.1 | 203.4±5.1 | 158.1±1.5 | 0.137±0.023 | 1.387±0.209 | 0.778±0.013 |
| Ritanserin 10 mg/kg | 2.1±0.1 | 30.6±4.6 | 10.5±3.9 | 200.9±21.3 | 138.4±28.2 | 0.074±0.014 | 0.317±0.087 | 0.691±0.115 |

Rats were injected i.p. with or without PCP (10 mg/kg) 1 hr after p.o. treatment with antipsychotics and then decapitated 1 hr after the injection of PCP. The frontal cortex was dissected out. The contents of monoamines and their metabolites were determined by HPLC with electrochemical detection. Each value represents the mean±S.E. from 3 to 4 rats. *P<0.05, **P<0.01 vs. the corresponding vehicle-treated group (Tukey test).
rearing, sniffing or turning was not altered by ritanserin (3 and 10 mg/kg). Both risperidone and ritanserin failed to alter the score for PCP-induced backpedalling (data not shown). As shown in Fig. 4B, the score for the PCP-induced head-twitch was significantly inhibited by both risperidone and ritanserin in a dose-dependent manner. The score of the head-weaving induced by PCP was so low that the effect of risperidone and ritanserin could not be determined (data not shown).

**Effects of risperidone, haloperidol and ritanserin on dopamine turnover and contents of 5-HT and 5-HIAA in rat brain**

As shown in Table 1, risperidone (2.4 mg/kg) and haloperidol (1.0 mg/kg), when they were administered alone or in combination with PCP (10 mg/kg), increased both the contents of DOPAC and HVA and the ratio of DOPAC to dopamine and HVA to dopamine in the striatum. The increasing effect of risperidone (2.4 mg/kg) on the contents of DOPAC (P<0.01) and the ratio of DOPAC to dopamine (P<0.01) in the striatum of PCP-treated rats was significantly lower than that of haloperidol (1.0 mg/kg). In contrast, risperidone (2.4 mg/kg) in combination with PCP increased both the contents of DOPAC and HVA and the ratio of DOPAC to dopamine in the frontal cortex, but the combination with haloperidol (1.0 mg/kg) did not (Table 2). Ritanserin (10 mg/kg) with or without PCP did not modify the contents of dopamine and their metabolites and dopamine turnover in either the striatum or frontal cortex (Tables 1 and 2). Moreover, both the contents of 5-HT and their metabolites and serotonin turnover in the striatum and frontal cortex were not modified by these antipsychotics, with the exception of haloperidol (1.0 mg/kg) in combination with PCP.

**DISCUSSION**

Many studies including our recent one suggested that dopaminergic neuronal systems play a very important role in the hyperlocomotion, rearing, sniffing, head-weaving and turning induced by PCP: 1) PCP-induced stereotyped behaviors are enhanced by amphetamine (23, 24), but attenuated by the dopamine-receptor antagonists haloperidol and pimozide (25, 26); 2) PCP produces significant locomotor stimulation and rearing when injected into the nucleus accumbens (27, 28), and this effect of PCP is inhibited by the systemic administration of haloperidol (27, 28); and 3) bilateral lesions of the striatum, made both electrically and by the dopaminergic neurotoxin 6-hydroxydopamine, reduce PCP-induced sniffing, head-weaving and turning, with the marked reduction of dopamine contents in the striatum (29, 30), while serotonergic neuronal systems also play an important role in PCP-induced head-weaving (8).

Our present results showed that risperidone, like haloperidol, inhibited PCP-induced hyperlocomotion and stereotyped behaviors such as rearing, sniffing, head-weaving and turning. Moreover, the oral dose levels of risperidone and haloperidol used in this study approximately equaled the 50% inhibitory doses for apomorphine-induced agitation of risperidone (approximately 1.8 mg/kg) and haloperidol (approximately 0.7 mg/kg) (31). Therefore, it is suggested that risperidone have inhibitory effects on such PCP-induced behaviors by blocking D2-receptors. These results are consistent with the following reports that risperidone inhibits both the stereotyped behavior and hyperactivity induced by the dopamine releaser amphetamine (32) and the agitation induced by the dopamine agonist apomorphine (31).

In vitro, PCP was found to inhibit the specific binding of [3H]-spiperone to 5-HT2A-receptors in a study using rat synaptic membrane (33, 34). Behaviorally, both PCP at a high dose (10 mg/kg, i.p.) and the 5-HT releaser p-chloroamphetamine induce head-twitch (Fig. 4, ref. 8). This head-twitch is enhanced 2 weeks after the injection of the 5-HT-neurotoxin, 5,7-dihydroxytryptamine with the increment of 5-HT2A-receptors (8). Furthermore, in rats that have received repeated administrations of PCP, tolerance is developed in the serotonergic neuronal system: the [3H]-spiperone binding capacity is reduced (34), and the frequency of PCP-induced head-twitch is decreased (15). These results suggest that PCP induces head-twitch via postsynaptic 5-HT2A-receptors. In the present experiments, the head-twitch induced by PCP (10 mg/kg) was blocked by the oral administration of risperidone (0.8 and 2.4 mg/kg) and ritanserin (10 mg/kg). The oral doses of risperidone and ritanserin used in this study seem to be high, because Janssen et al. (18) have reported that the 50% inhibitory s.c. doses of risperidone and ritanserin on 5-hydroxytryptophan-induced head-twitch was 0.016 and 0.074 mg/kg, respectively. These discrepancies resulted from the differences of the drug and observational time; that is, they only observed the effects over a 20-min period, starting from 70 min after the 5-hydroxytryptophan injection, but we observed the head-twitch over a 90-min period, starting from immediately after the PCP injection. Rinaldi-Carmona et al. (21) have shown that ritanserin (10 mg/kg, p.o.) inhibits the head-twitch induced by the 5-HT2A-agonist (±)DOI, supporting that our oral dose levels of ritanserin is appropriate for the determination of its inhibitory effects on PCP-induced head-twitch. Thus, our present results suggest that risperidone may inhibit the PCP-induced head-twitch by blocking 5-HT2A-receptors.

PCP-induced backpedalling is diminished by lesions of
over. Recently, several investigators have demonstrated that sigma-receptors may be involved in dopamine turnover. Haloperidol and phencyclidine can bind to sigma-receptors should be carried out. Secondly, because HT2A-receptors on dopamine turnover, further investigations should be made. Therefore, with regards to the roles of 5-HT2A-receptors other than 5-HT2A-receptors may be more important in inducing the backpedalling.

In the neurochemical study, risperidone increased the degree of dopamine turnover, similarly to haloperidol, in both the striatum and frontal cortex, while the effects of risperidone in combination with PCP on the contents of DOPAC and the ratio of DOPAC to dopamine in the striatum were significantly lower than that of haloperidol in combination with PCP. Since Leysen et al. (35) have reported that the in vitro binding affinity of risperidone and haloperidol for D2-receptors was exactly the same in prepared membranes from rat striatum and frontal cortex, it is possible that the binding capacity of risperidone and haloperidol to other kinds of receptors may be responsible for the differences of dopamine turnover in the striatum.

Two possibilities may underlie these differences between risperidone and haloperidol. First, since risperidone binds to 5-HT2A-receptors more preferentially than D2-receptors (17), it is possible that 5-HT2A-receptors may play an important role in dopamine turnover. However, there are few reports about the interaction between D2-receptors and 5-HT2A-receptors in dopamine turnover (35, 36), and it is difficult to compare our present results to previous ones. For example, Leysen et al. (35) have reported that there are some differences of the effects on dopamine and their metabolites in rat brain between risperidone and haloperidol, although the doses of these antipsychotics used in their study were higher than the doses that have an inhibitory effect on both dopamine and serotonin-mediated behaviors (18, 31, 32); that is, the dose of haloperidol leading to maximal HVA levels in the striatum is almost equal to the dose producing 50% occupation of D2-receptors, whereas the dose of risperidone is about 2 times higher than the 50% occupation dose. Saller et al. (36) have reported that the 5-HT2A-receptor antagonist ICI 169,369 enhanced the increase of dopamine metabolite levels induced by haloperidol in the striatum, although these results are inconsistent with our present results. Therefore, with regards to the roles of 5-HT2A-receptors on dopamine turnover, further investigations should be carried out. Secondly, because haloperidol and phencyclidine can bind to sigma-receptors (37, 38), but risperidone can not (35), it is possible that sigma-receptors may be involved in dopamine turnover. Recently, several investigators have demonstrated that sigma-receptors may play an important role in schizophrenia (37, 39) and that some of the sigma-receptor ligands have the ability to change dopamine turnover (40, 41). Moreover, phencyclidine-induced head-weaving, which is partly mediated by nigrostriatal dopaminergic neuronal systems (29, 30), was blocked by the sigma-receptor antagonists NE-100 and BMY-14802 (42, 43). Therefore, it is possible that our present results may result from the differences in the binding affinity for sigma-receptors between risperidone and haloperidol, although the roles of sigma-receptors on dopamine turnover remain to be further elucidated.

Thus, these neurochemical results taken together with our present behavioral results suggest that risperidone has the same inhibitory effects on PCP-induced behaviors as haloperidol with lower increasing effects on dopamine turnover in the striatum than haloperidol. The nigrostriatal dopaminergic neurons and mesolimbic dopaminergic neurons are thought to be involved in the expression of the extrapyramidal side effects and therapeutic effects of antipsychotics, respectively (9, 44). Risperidone is useful for the treatment of schizophrenia because it has lower extrapyramidal side effects than other antipsychotics in humans (19). Therefore, it is possible that the differences of the present biochemical findings between risperidone and haloperidol may indicate that risperidone has clinical advantages over haloperidol because it has less extrapyramidal side effects. Because it has been reported that other neuronal systems, including cholinergic ones, may be involved in the extrapyramidal side effects (45-47), the effects of these drugs on the other neuronal systems should be further investigated.

In conclusion, it is clear that risperidone can inhibit PCP-induced stereotyped behaviors in rats, and this effect is mediated by the blockade of both D2-receptors and 5-HT2A-receptors. Therefore, these results suggest that risperidone may have potent antipsychotic effects on schizophrenia as well as PCP psychosis in humans.

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